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THE ACETONE BODIES OF THE BLOOD AFTER MORPHINE AND AFTER ETHER ANAESTHESIA

By

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A considerable increase in the amount of acetone bodies in the blood has only one general pathological interpretation and that is a condition of acidosis or what may be termed the acetone complex. This term implies the anomally wherein fats instead of being burned completely are in part eliminated as acetone, acetoacetic and beta oxybutyric acids.

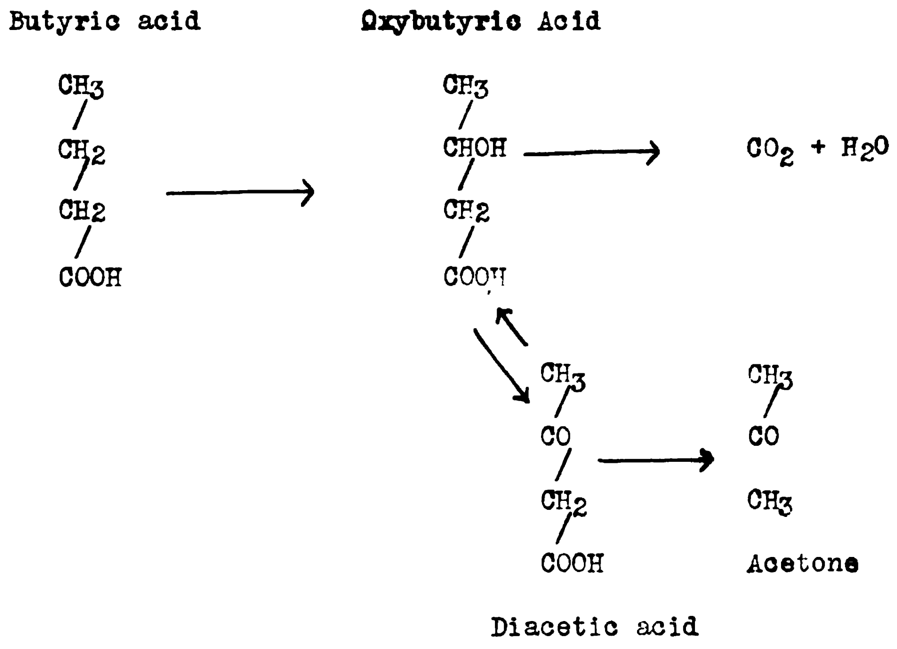
Observations by Brugsch(1) showed an abundant excretion of acetone bodies in the case of a professional faster who had an extensive fatty panniculus and the complete absence of any acidosis in an emaciated woman who had not the slightest visible trace of body fat. There has not as yet been recognized any connection between the excretion of acetone bodies and the reduction of body protein. Magnus-Levy(2) showed in a case of "acidosis" that the large amount of acetone bodies excreted exceeded the amount of oxybutyric acid that could be formed if the total carbon of the coincident protein destruction were converted into oxybutyric acid. Therefore, the acetone bodies must have been derived from fat and not from protein considering the amount and under the circumstances under which the complex occurs as a pathological variation. Magnus-Levy(2) has also shown that the acetone bodies are not derived from carbohydrates, because of the greater quantity of the former.

The ingestion of dietary fat has been noted by Joslin(3) to result in an increased excretion of acetone bodies. Knoop and Embden(4) have pointed out that in the catabolism of the normal fatty acids there

is a two by two loss of carbon atoms from the carboxyl end. This continuous shortening would result in the formation of butyric acid, from which oxybutyric acid forms, and from this then diacetic acid and acetone.

Observations by Bär and Blüm(5) showed an increase in the elimination of acetone bodies after the administration of butyric acid and caproic acid to animals.

Otto Neubauer(6) suggests that butyric acid goes over to oxybutyric acid, which is believed to be an intermediate product of physiological metabolism. His schema may be represented as follows:



In normal individuals oxybutyric acid is oxidized to carbon dioxide and water. Any interference with this normal process would result in the oxybutyric acid going over to diacetic acid and then acetone by the splitting off of carbon dioxide.

The passage of oxybutyric acid into diacetic acid is a reversible process. A decrease in the oxidation processes of the body due to a

diminished oxygen supply in the blood or to diminished oxidation activities in the tissues would therefore result in the formation of diacetic acid and acetone increasing the total amount of acetone bodies. This condition would tend to exist until the normal oxidation processes were resumed.

The increased acetone bodies would tend to react with the sodium bicarbonate and disodium phosphate forming a sodium salt which is neutral in reaction, monosodium phosphate, a slightly acid salt, and free carbonic acid. Hence a lowering of the alkalai reserve of the body results and therefore a state of acidosis exists. The hydrogen ion concentration of the blood is slightly changed due partly to the small degree of ionization the carbonic acid and acid phosphate undergo.

The increased amounts of acids resulting from these accumulating waste products stimulate the respiratory center and therefore increased ventilation of the lungs results as is shown by the rise after the sixth hour in the accompanying respiration curve. Work was done on the blood sugars in the morphine series of experiments. The filtrate obtained after removal of the proteins by precipitation with mercuric sulfate was used in the procedure. A modification of Benedict's method was devised in which the mercuric sulfate was removed by hydrogen sulphide saturation.

Although a uniform increase in the blood sugars was obtained, not sufficient data was secured and it was found that the hydrogen sulphide could not be removed in some cases successfully by boiling.

The reducing action of hydrogen sulphide would naturally reduce some of the sugars so that the amount of picric acid used would not be quantitatively an index of the reducing agents present in the solution. This fact was discovered after a number of samples had been determined and for this reason not much reliability can be placed on the reports.

A control animal was run through the routine of the procedure employed except for the administration of morphine and anaesthesia to determine if any changes would occur in the alkalai reserve, hydrogen ion concentration and acetone bodies due to excitement etc. A minimal injection of cocaine was made over the right femoral artery. The dog remained on the board used during the entire time of the experiment and the slight changes observed in the blood examination were negligible.

Experimentation carried on in the University of Wisconsin Physiological laboratories demonstrated a condition of "acidosis" after morphine. The accompanying composite curve indicates a decreased alkali reserve after morphine administration. This series of experiments were performed to determine if the condition of acidosis could be due to pathological fat metabolism. Experiments were carried on simultaneously to demonstrate the effect of morphine on respiration, alkalai reserve, and hydrogen ion concentration. By a comparison of the curves obtained the rate of formation of acetone bodies and their subsequent oxidation may be interpreted.

Another series of experiments was performed to determine the effect of ether anaesthesia on the acetone bodies of the blood.

An investigation of the literature on pathological metabolism after morphine and ether anaesthesia yields practically no information. Nothing could be found concerning the actual time element in the rate of formation and oxidation of the intermediary products of fat metabolism.

Method

The experiments were performed on dogs whose weights varied from 5 to 15 kilos. The femoral artery was exposed under local anaesthesia (cocaine 5 cc. of 0.5 per cent solution) and a cannula inserted. A 10 cc. sample of normal blood was withdrawn. The method of Van Slyke and Fitz for the determination of the acetone bodies, B-hydroxybutyric acid, aceto-acetic acid and acetone was followed.

The 10 cc. of whole blood were diluted with 100 cc. of water in a 250 cc. flask, and 20 cc. of 10 per cent mercuric sulfate were added. The solution was shaken for a moment, until the protein coagulated, and was then diluted with water up to the 250 cc. mark. After 15 minutes it was filtered through a dry folded filter. The blood was not diluted with more than ten volumes of water before the mercury was added because coagulation of the proteins would have been considerably slower, - hence the reason for not completing the dilution until after the coagulation had occurred.

125 cc. of the filtrate, equivalent to 5 cc. of the blood were placed in a 500 cc. Erlenmeyer flask. 10 cc. of 50 per cent sulfuric acid and 35 cc. of 10 per cent mercuric sulfate were added. The flask was connected with a reflux condenser having a straight condensing tube of 8 mm. diameter and heated to boiling. After boiling began 5 cc. of 5 per cent potassium dichromate solution were added through the condenser tube. Boiling was continued gently for 1½ hours. A yellow precipitate formed consisting of the mercury sulfate - chromate compound of the preformed acetone, and of the acetone which had been formed by decomposition of acetoacetic acid and by oxidation of the hydroxybutyric acid. The precipitate was collected in a Gooch crucible, washed with 200 cc. of cold

water, and dried for an hour at 110°. The crucible was allowed to cool and weighed. The reagents used were tested by running a complete acetone bodies determination on a sample of distilled water. No precipitate was obtained.

One gram of precipitate is equal to 12.8 gm. of total acetone bodies calculated as grams of acetone per liter of blood. A control dog was run to determine whether any changes in amounts of acetone bodies might occur due to fright etc. during the experiments.

In one series of dogs subcutaneous injection of morphine was made, 10 mgms. per kilo weight of each dog immediately after the sample of normal blood was withdrawn.

In another series of dogs deep ether anaesthesia was given with no morphine. Samples of blood, 10 cc. each, were withdrawn at regular intervals from both series and the same method used to determine the total acetone bodies as that described for the normal sample.

Alkalai reserve, H ion concentration and respiration determinations were made on the same dogs.

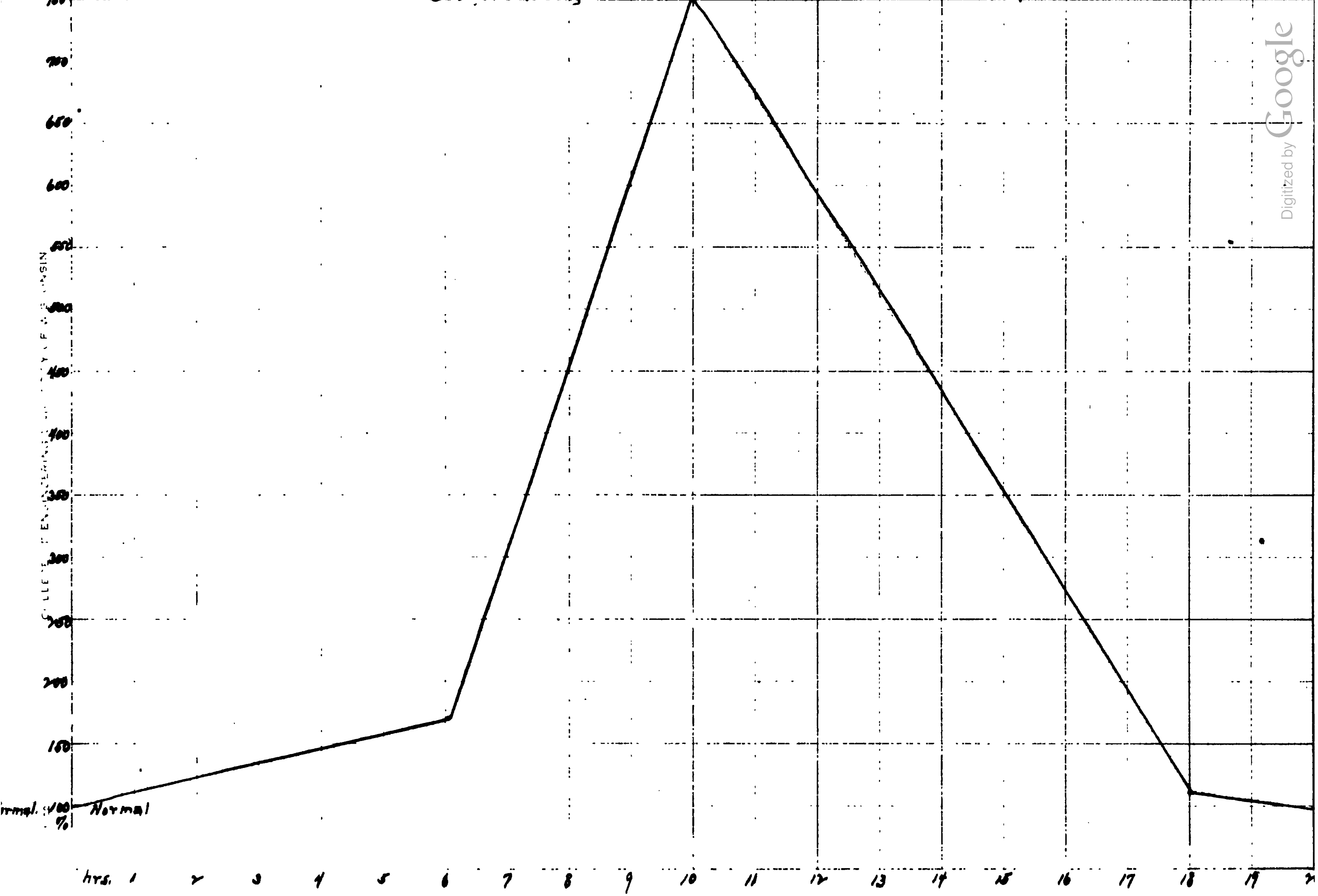
Results

Acetone Bodies Composite

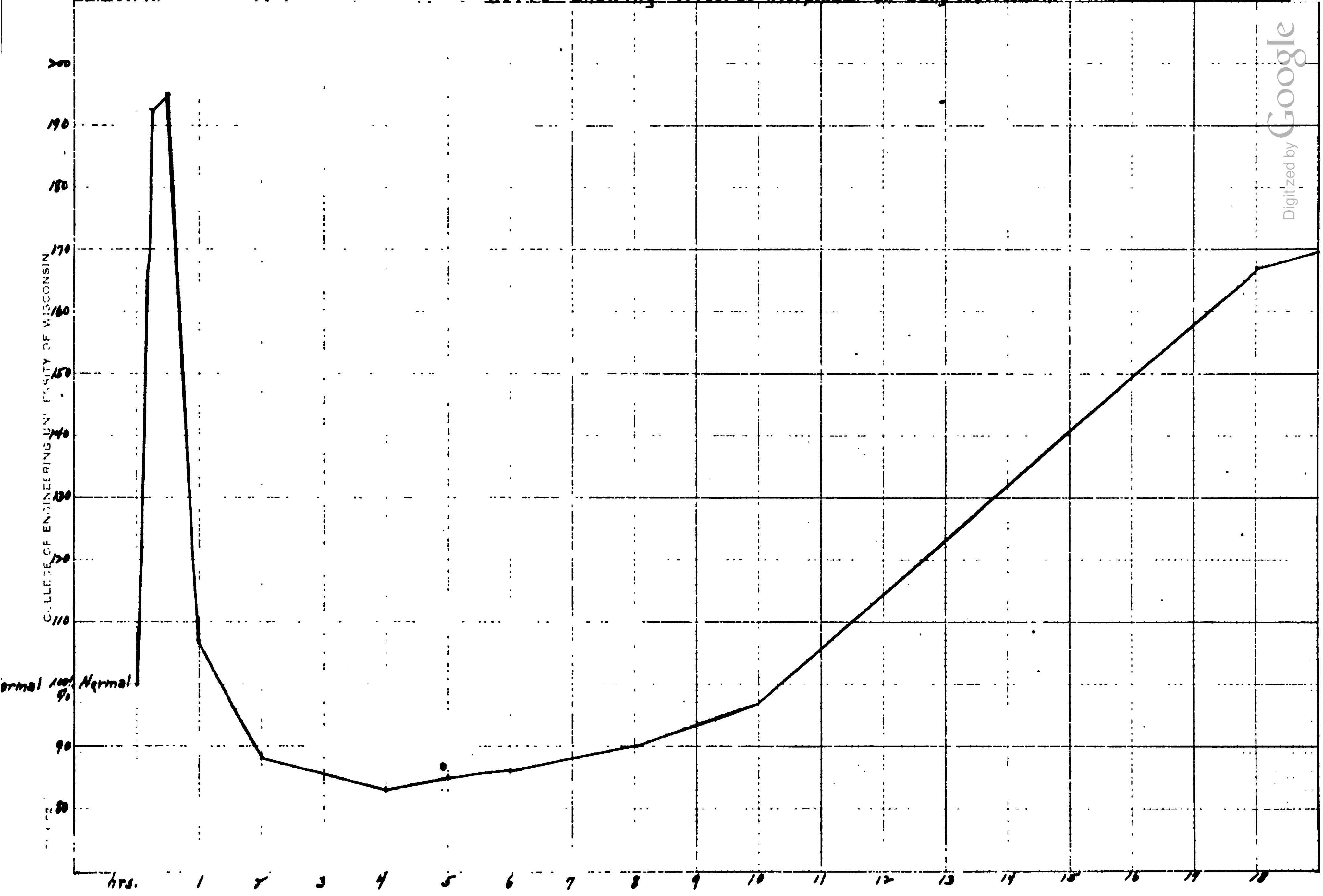
Exp. No.	Normal	6 hrs.	10 hrs.	18 hrs.
20	.0395 gms.	.0514		.0097
22	.0256	.0780		.0460
30	.0499		.0588	
31	.0313	.0313	.4150	.0550
19	.0196	.0524		
Average:	.0332	.0533	.2369	.0369
	100%	170%	750%	111%

.0332 gms. per liter = 100% normal

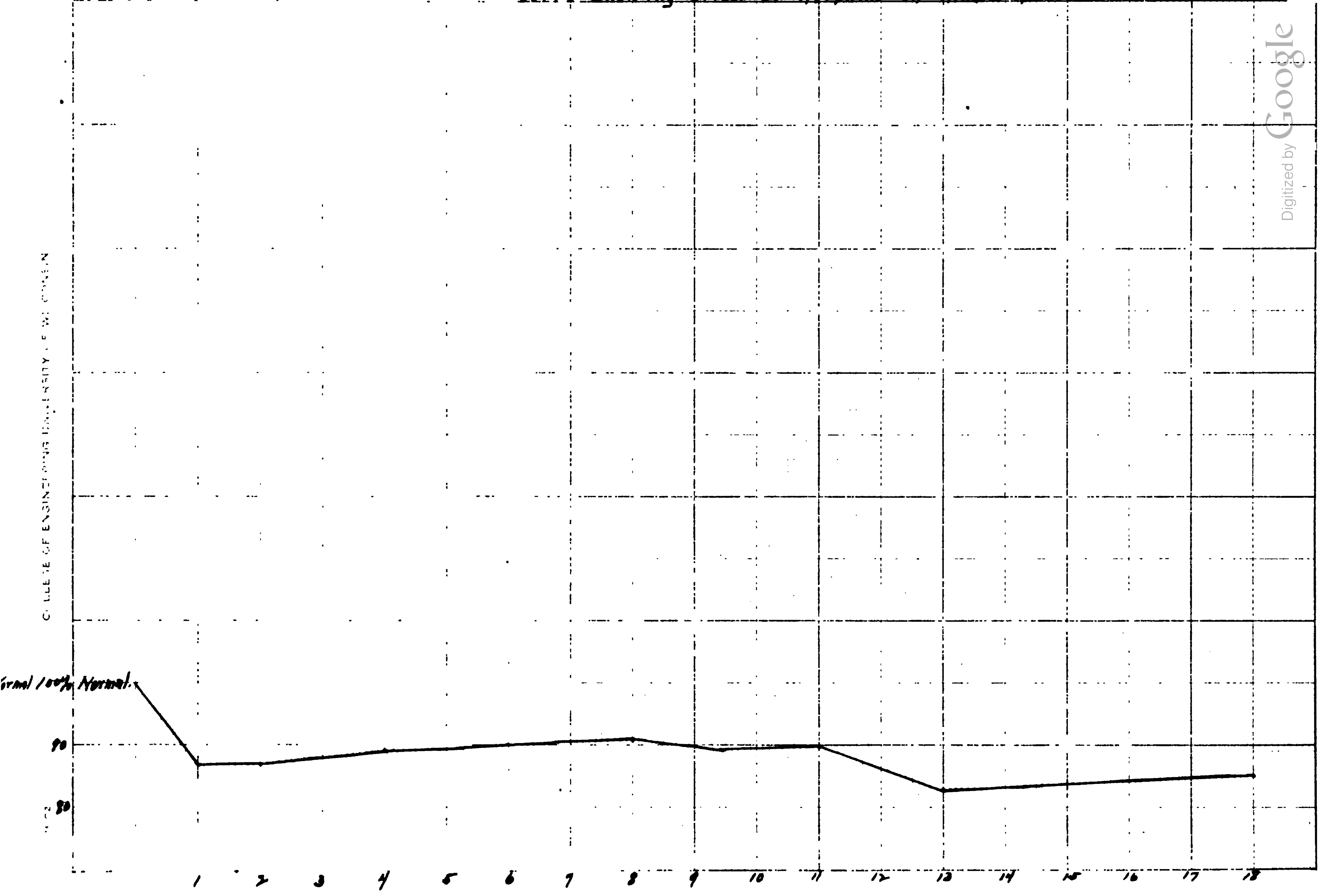
Curve showing amounts of Acetone Bodies after Morphine.



Curve showing effect of Morphine on Lung Ventilation.



Curve showing effect of Morphine on Alkalai Reserve



Ether Anaesthesia

Exp. No.	Normal	7 hrs.	9 hrs.
23	.05632 gms.	.02048	
24	.04608	.03072	.0128
25	.05248	.04736	
Atypical 35	.0384	.00192	

Control Exp. minimal injection of cocaine over femoral

	Normal	3 hrs.	11 hrs.	19 hrs.
34	.0128	.01024	.01152	.01536

Interpretation of Results

The accompanying composite curve for the acetone bodies indicates a slight increase from the first to sixth hours. From the sixth to tenth hours there is a great increase, after which they return to normal amounts at the eighteenth hour.

The respiration curve indicates a decrease in respiration after the first hour and this continues until the tenth hour. During this period there must be decreased oxidation processes in the tissues thus allowing the accumulation of acetone bodies. The increased respiration after the tenth hour, resulting in increased oxidation processes may explain the decrease in the accumulated acetone bodies to normal. However, on account of the great amount of acetone bodies and their rapid disappearance it seems that some other factor besides oxidation is responsible for this rapid change to normal. The acetone bodies may have reached their threshold valve in the kidney and were excreted. No urine analysis was made and this factor cannot be considered at present.

The decrease in acetone bodies after ether anaesthesia can be interpreted in several ways since no attempt was made to determine the factor

causing such a change. The interpretations for this reason are purely hypothetical.

The ether may have united chemically with the acetone bodies and resulted in their being more easily oxidized. Ether may stimulate the ordinary oxidation processes of fats.

Decreases in alkalai reserve were observed in the same animals and an increased hydrogen ion concentration noted. The bicarbonate fall may be due to the formation of some as yet unidentified organic acids resulting from disturbances in metabolism or merely to a shift of bicarbonate from plasma to tissue cells under the influence of overstimulated respiration.

Summary

Morphine administration results in an increase in the acetone bodies of the blood in ten hours to 750 per cent their normal amounts.

This condition may account for the "acidosis" produced by morphine administration.

Ether anaesthesia results in a decrease of the acetone bodies, for which the explanation is unknown at present.

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